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Regulation of Lymphocyte Function by Adenosine

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Abstract

Adenosine regulates the interaction between lymphocytes and the vasculature and is important for controlling lymphocyte trafficking in response to tissue injury or infection. Adenosine can blunt the effects of T cell receptor (TCR) activation primarily by activating adenosine A_{2A} receptors ($A_{2A}R$) and signaling via cyclic AMP and protein kinase A (PKA). PKA reduces proximal TCR signaling by phosphorylation of C-terminal Src kinase (Csk), nuclear factor of activated T cells (NF-AT) and cyclic AMP response element binding protein (CREB). PKA activation can either enhance or inhibit the survival of T cells depending on the strength and duration of signaling. Inducible enzymes such as CD73 and CD39 regulate adenosine formation and degradation *in vivo*. The extravasation of lymphocytes through blood vessels is influenced by $A_{2A}R$-mediated suppression of Intercellular Adhesion Molecule 1 (ICAM) expression on lymphocytes and diminished production of IFNγ and IFNγ-inducible chemokines that are chemotactic to activated lymphocytes. Adenosine also decreases the barrier function of vascular endothelium by activating $A_{2B}Rs$. In sum, adenosine signaling is influenced by tissue inflammation and injury through induction of receptors and enzymes and has generally inhibitory effects on lymphocyte migration into inflamed tissues due to PKA-mediated effects on adhesion molecules, IFNγ production and endothelial barrier function.

Keywords

adenosine; lymphocytes; T cells

Introduction

In addition to playing a central role in biochemical processes, adenosine is a generally anti-inflammatory[1, 2] signaling molecule that is produced by all cells in proportion to metabolic activity, injury and hypoxia. Adenosine signaling is mediated by four G-protein coupled adenosine receptors (AR): A_1, A_{2A}, A_{2B} and A_3[3]. These receptors are antagonized by naturally occurring and widely consumed methylxanthines, caffeine and theophylline, as well as by more potent synthetic antagonists[3, 4]. Adenosine produced as a byproduct of metabolic activity readily crosses most cell membranes on nucleoside transporters[5].

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Disclosures

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Extracellular adenosine is produced from the degradation of adenine nucleotides by exonucleases. ATP and ADP are converted to AMP and adenosine following nucleotide release to the extracellular space through membrane channels[6], necrotic cell death, or as granular components of platelets, mast cells and neuronal synaptic granules.

The $A_{2A}R$ is the predominant adenosine receptor subtype found on lymphocytes. Stimulation of $A_{2A}Rs$ on activated T cells acutely inhibits pro-inflammatory cytokine production and effector functions[7, 8]. In addition, both A_{2A} and A_{2B} receptors are found on antigen presenting cells (APCs) and strongly influence T cell activation. This review focuses on recent advances in our understanding of lymphocyte activation and the interaction of lymphocytes with the vasculature by enzymes that regulate adenosine metabolism, adenosine receptors, and cyclic AMP signaling.

Lymphocyte Activation

T cells can be activated as a result of antigen presentation by antigen presenting cells (APCs) such as dendritic cells (DCs) or macrophages. Antigenic molecules are displayed on the surface of APCs by major histocompatibility proteins (MHC) and activate T cell receptors on lymphocytes (Figure 1). Following TCR stimulation, lymphocyte activation can result in T cell differentiation, cytokine production, or cytotoxic activity. Antigens are presented by APCs to the ligand-binding portion (αβ subunits) of T cell receptors (Figure 1). TCR activation, known as “signal 1”, is transduced through γ,δ,ε and ζ chains of the CD3 portion of the TCR. Following stimulation, TCR signal transduction is initiated by lymphocyte-specific protein tyrosine kinase (Lck) phosphorylation of tyrosines on immunoreceptor tyrosine-based activation motifs (ITAMs) present in the tails of CD3 components. These phosphorylated residues provide docking sites for the SH2 domains of zeta-chain-associated protein kinase 70 (ZAP-70), which dock and phosphorylate tyrosines on Linker of Activated T cells (LAT). In the case of a small subset of lymphocytes known as invariant natural killer T (iNKT) cells, lipid antigens replace peptide antigens on APCs, and MHC is replaced by CD1 antigen presenting molecules[9]. Below we discuss how T cell activation influences lymphocyte adhesion to the endothelium and the production of chemotactic chemokines.

Adenosine $A_{2A}R$ activation selectively inhibits cytokine production by T cell subsets

Depending on the environment during antigen encounter, CD4+ T cells can differentiate into T helper 1 cells (Th1) that secrete primarily type 1 cytokines including interleukin 2 (IL-2), interferon γ (IFN-γ) and TNFα; T helper 2 cells (Th2) that secrete primarily IL-4, IL-5, and IL-10; or Th17 cells that secrete IL-17A, IL-17F and IL-21. Type 1/type 2 cytokine polarization exists for both MHC class 2-restricted $CD4^+$ T cells (Th1/Th2 subsets) and for MHC class 1-restricted cytotoxic $CD8^+$ T cells (Tc1/Tc2 subsets). Agonist binding to $A_{2A}Rs$ activates the heterotrimeric G protein, Gs, to catalyze cyclic AMP production. The protein kinase A (PKA) pathway negatively regulates the production of type 1 cytokines, with lessor effects on type 2 cytokines[10]. $A_{2A}R$ activation reduces production of IL-2, TNFα and IFNγ secretion from Tc1 and Tc2 cells, but does not affect IL-4 or IL-5 secretion[11].

$A_{2A}R$ activation also strongly inhibits the production of IFNγ by iNKT cells.[12] $A_{2A}R$ activation has not been reported to directly influence cytokine release from purified Th-17 cells. When given *in vivo* or in mixed cell T cell development assays with antigen presenting cells, A_{2A} agonists inhibit production of IL-6 and enhance production of IL-10. This results in indirect inhibition of Th1, Th2 and Th17 effector cell development.[13, 14]. In sum, the strongest direct effects of $A_{2A}R$ stimulation on lymphocytes is on type 1 cytokine production by Th1, Tc1 and iNKT cells[8, 11, 12].

How Cyclic AMP and PKA mediate $A_{2A}R$ signaling in T cells

The activation of Gs following agonist binding to $A_{2A}Rs$ stimulates adenylyl cyclase to produce cyclic AMP. Two downstream effectors, protein kinase A (PKA) and Exchange protein directly activated by cyclic AMP (Epac), are the principal mediators of cyclic AMP action in T cells. The cyclic AMP mimetic, 8-(4-chlorophenylthio)adenosine-3′,5′-cyclic monophosphate (8-CPT-cAMP) is a useful tool for distinguishing between these two pathways because it activates PKA but fails to activate Epac. Experiments using 8-CPT-cAMP indicate that most transcriptional effects of cyclic AMP in T cells are mediated by PKA. In addition to adenosine, several other Gs coupled receptors are found on T cells. These include β2-adrenergic[15], prostaglandin E2 (PGE2), dopamine D1[16] and vasoactive intestinal peptide (VIP)[17]. Adenosine is particularly important for limiting lymphocyte activation because $A_{2A}Rs$ are induced upon activation of T cells[8, 18] and iNKT cells[19]. Cyclic AMP is degraded in T cells primarily by phosphodiesterase 4 (PDE4) and PDE4 inhibitors facilitate the actions of adenosine and other Gs-coupled receptor agonists.

Cyclic AMP regulates T cell cytokine secretion and proliferation by directly phosphorylating the transcription factors cAMP response element binding protein (CREB) and nuclear factor of activated T cells (NF-AT).[20] Suppression of proximal T cell signaling pathways indirectly inhibits activation of another transcription factor, nuclear factor kappa B (NF-κB). The most abundant isoform of PKA found in T cells, PKA-1, activates C-terminal Src kinase (Csk), which inhibits the Src family tyrosine kinases Lck and Fyn and thus functions to check T cell activation (Figure 1). PKA-1 is targeted to the TCR-CD3 complex during T-cell activation via an A-kinase-anchoring protein (AKAP) that serves as a scaffold for the cAMP-PKA/Csk pathway in lipid rafts of the T cell plasma membrane. The small GTP binding protein RhoH also serves as an adaptor molecule for Lck and Zap-70 to regulate TCR signaling[21]. Protein kinase C theta (PKCθ) and PKA inversely affect cytokine expression, whereas other PKC isotypes do not influence TCR signaling. The opposing cAMP/PKA and PKCθ pathways converge at the level of NF-AT[22]. NF-AT proteins are retained in the cytoplasm following serine phospyorylation by PKA. After T cell activation, NF-AT proteins are dephosphorylated by the Ca^{2+}-calmodulin activated protein phosphatase calcineurin. This dephosphorylation unmasks a nuclear localization signal, facilitating the rapid translocation of NF-AT proteins to the nucleus where they pair with AP-1 and bind to consensus NF-AT sites on DNA. The immunosuppressive drugs cyclosporin A and FK506 prevent the calcineurin-mediated dephosphorylation of NF-AT, accounting for some of their immunosuppressive effects on T cells. PKA also regulates T cell function at the level of other transcription factors and kinases including members of the mitogen-activated protein kinase pathway, RhoA and proteins involved in the control of cell cycle progression.[23]

Signal 2 and cAMP

Signal 1 activation of TCRs alone produces limited T cell activation because TCR engagement locally enhances cyclic AMP production and activates Csk in the region of the immunologic synapse. Activation of TCRs is amplified by signal 2, i.e. co-stimulation of CD28 by ligands expressed on the surface of APCs, B7.1 and B7.2 (CD80 and CD86). Upon TCR/CD28 co-stimulation PI3K activation leads to phosphatidylinositol-(3,4,5)-triphosphate (PIP3) production. This stimulates recruitment of an AKT/β-arrestin/PDE4 complex to the plasma membrane via the AKT plextrin homology (PH) domain, resulting in the degradation of cyclic AMP located near lipid rafts[24, 25] It is not entirely clear how stimulation of the TCR results in elevated cAMP levels[26], but recruitment of Gs to lipid rafts may be involved[27]. It is also possible that cell activation due to TCR signaling stimulates production of adenosine that exits the cell to act on autocrine or paracrine A_{2A} receptors.

Adenosine signaling increases T cell tolerance and Treg development

Unlike the localized production of cyclic AMP that occurs as a result of signal 1, strong activation of A_{2A}Rs or other Gs-coupled receptors can produce whole cell increases in cyclic AMP that are not limited just to the region of lipid rafts. Thus, extracellular adenosine reduces the activation of T cells by APCs and modifies T cell differentiation, cytokine production and proliferation by preventing rapid tyrosine phosphorylation of ZAP-70 and downstream signaling such as activation of Akt and ERK1/2.[28] Cyclic AMP elevation in naïve T cells also favors development of a regulatory phenotype (Treg) characterized by high expression of CD25, cytotoxic-T-lymphocyte-associated protein 4 (CTLA4), and Forkhead box protein 3 (FoxP3). CTLA4 is involved in suppressive activities by Tregs.[29] Unlike T effector cells, Tregs also express ecto-enzymes CD39 and CD73 (Table 1) that metabolize adenine nucleotides in the extracellular space to adenosine that locally inhibits the activation of effector T cells and APCs.[7]

Paradoxical effects of PKA on T cells survival

Inhibition of apoptosis

Activation-induced cell death (AICD) describes an apoptotic program initiated by restimulation of previously activated peripheral T cells. A_{2A}R activation reduces AICD in mouse CD4+ hybridomas and human Jurkat cells.[30] A_{2A}R activation reduces AICD by interfering with the production of factors that stimulate T cell activation, IL-2-and the downstream expression of the co-stimulatory molecules CD2 and CD28.[31]

Enhancement of apoptosis

In contrast to the anti-apoptotic effect of transient cyclic AMP elevation, prolonged elevation of cyclic AMP triggers T cell apoptosis. This property of persistent cyclic AMP elevation to kill T cells has been used to select for T cell lines that have mutations in the cyclic AMP signaling pathway[32]. Recent studies have identified the mechanism by which cyclic AMP triggers an apoptotic program in T cells. Treatment of wild type S49 T cells with the PKA activating cyclic AMP analog, 8-CPT-cAMP, increases the expression of cytotoxic T lymphocyte antigen-2α (CTLA-2α), a cathepsin L-like cysteine protease

inhibitor that triggers apoptosis[33]. Treatment of kinase- S49 cells T cells that lack functional PKA, with 8-CPT-cAMP fails to stimulate CTLA-2α expression and apoptosis, indicating that the increase in CTLA-2α in wild type S49 cells is PKA-dependent[34,35].

Effects of adenosine deaminase deficiency on T cell survival

Several investigators have sought to determine if PKA-mediated killing of T cells contributes to severe combined immunedeficiency (SCID) that occurs in individuals lacking adenosine deaminase (ADA). Since ADA deficiency causes adenosine concentrations to increase in the thymus and other tissues, it is reasonable to suspect that the resulting increase in $A_{2A}R$ signaling via adenosine, Gs and PKA in thymocytes might evoke T cell killing by PKA-induced apoptosis. Apasov et al[36] concluded that a portion of thymocyte apoptosis that occurs in response to ADA deficiency can be attributed to $A_{2A}R$ activation. However, the primary cause of toxicity in developing human thymocytes is the accumulation of deoxyATP which triggers mitochondrial-dependent apoptosis.[37]

CD26 dampens adenosine signaling in T cells

In human cells a soluble form of adenosine deaminase (ADA) can bind to cell surface CD26 that is expressed by lymphocytes, epithelial cell and capillary endothelial cells. CD26 expression is strongly up regulated following T cell activation[42]. ADA binding to CD26 on human T cells results in ADA accumulation on the T-cell surface and is associated with T cell activation.[43]

Effects of adenosine metabolism and transport on lymphocyte activation

The concentration of adenosine in the extracellular space is regulated by adenosine transport as well as adenosine formation and degradation (Table 1). Nucleoside transporters are divided into two families; the Na^+-dependent solute carrier family 28 (SLC28) and the equilibrative solute carrier family 29 (SLC29). SLC28 family transporters (CNT1-3) display subtype-selective expression patterns; CNT1 is localized primarily to epithelial tissues whereas CNT2 and CNT3 have more widespread distributions. SLC29 family transporters (ENTP1-4) are glycosylated proteins localized to the plasma and mitochondrial membranes. They are expressed in the heart, brain, mammary gland, erythrocytes and placenta, and also in fetal liver and spleen, and mediate nucleoside influx and efflux. Insulin and glucose induce changes in expression levels of nucleoside transporters in T lymphocytes.[38]

Lymphocyte CD39 and CD73 and immune regulation

T regs comprise a subset of T cells that inhibit the activation of effector T cells. CD39 (ENTP1) and CD73 (5NTD) are coexpressed on the surface of murine T regulatory but not effector cells, and together generate extracellular adenosine from ATP, ADP and AMP. Murine T regulatory cells are usually defined based on expression of CD4, CD25, and the transcription factor, FoxP3. However, these markers are not sufficient to uniquely define T cell subsets in humans. Liu et al[39] found that the IL-7 receptor (CD127) is low on a subset of CD4+ T cells in peripheral human blood. CD39, independently of CD73, is expressed on human CD4+ CD25+ CD127lo Tregs, also characterized by high expression of Foxp3. A distinct population of human CD4+ CD39+ T lymphocytes does not express CD25 and

FoxP3. The latter cells secrete proinflammatory cytokines such as IFNγ and IL-17. These cells are increased, with a concomitant decrease in Tregs, in the peripheral blood of patients exhibiting transplant rejection. Hence, CD39 may be a useful marker for the success of organ transplantation.[40] Immunodeficiency from HIV is associated with a significant increase in CD39 expression on human T regs[41]. Treg inhibitory effects are enhanced by CD39 up regulation, and are replicated by activation of A_{2A}Rs on HIV patient T cells. A_{2A}Rs are expressed at higher than normal levels on the T cells of HIV patients. The expansion of CD39+ Treg cells correlates with the level of immune activation and low $CD4^+$ T cell counts in HIV. A genetic association study identified a CD39 gene polymorphism that is associated with down-regulation of CD39 expression and slower progression to AIDS[41].

Adenosine regulation of APCs

Independent of the effects of adenosine on T cells, dendritic cells and macrophages are highly susceptible to adenosine-mediated regulation. DCs and macrophages activated by LPS in the presence of adenosine have a reduced capacity to induce Th1 polarization of naive CD4+ T lymphocytes, diminished release TNFα and IL-12, and enhanced release of anti-inflammatory IL-10[44–48]. Inhibition of adenosine receptor signaling is needed to observe optimal activation of DC's and T cell activation by pathogen-associated molecular patterns[49, 50]. DCs express all four types of adenosine receptors but their expression level varies depending on subtype, maturation status or progenitors from which they differentiate[51–55]. Immature DCs express A1 and A3 adenosine receptors[52–54] that are thought to mediate chemotaxis[53]. In LPS-matured DCs A1 and A3 receptors are down regulated while A_{2A} and A_{2B} receptors are up regulated[51–55]. A_{2B}R expression can be further induced by hypoxia[51] or TNFα[56]. A_{2B}R activation also inhibits DC-mediated T cell activation because A_{2B}R stimulation reduces LPS-induced surface expression of MHCII and CD86 which results in decreased IL-2 expression by T cells [57]. However, activation of the A_{2B}R can be pro-inflammatory. In the absence of TLR signaling A_{2B}R stimulation increases pro-inflammatory IL-6, which together with TGFβ can deviate naïve CD4+ T cells to a Th17 phenotype that favors chronic inflammation[58].

Interface between lymphocytes and the Vasculature

Adenosine and ischemia

Vascular diseases, infections or tissue injury can lead to vaso-occlusion and tissue hypoxia that strongly influences adenosine signaling to immune cells. Part of this effect is due to inhibition of adenosine kinase in hypoxic cells, resulting in an increase in the cellular accumulation of adenosine[59]. In addition, hypoxia inducible factor (HIF) drives induction of immunosuppressive A_{2B} receptors on APCs[60] and CD73 on epithelial and endothelial cells[61, 62]. Elevated levels of CD73 produce elevated tissue and blood levels of adenosine due to enhanced conversion of AMP to adenosine.

Adenosine and ICAM-1

Tissue damage due to trauma or infection produces an inflammatory cascade resulting in chemotaxis into the inflamed tissue of lymphocytes and other leukocytes. Adenosine can

inhibit this process. Part of the effect of adenosine has been attributed to inhibition of expression of intercellular adhesion molecule 1 (ICAM-1).[63] ICAM-1 is expressed by T cells and can bind to macrophage adhesion ligand-1 (Mac-1), leukocyte function associated antigen-1 (LFA-1), and fibrinogen, all of which are expressed on endothelial cells and other leukocytes.

Adenosine and IFNγ-inducible chemokines

Chemokines contribute to lymphocyte extravasation into inflamed tissues. Tissue damage results in the activation of invariant natural killer T (iNKT) cells that rapidly produce large amounts of IFN-γ upon activation[12]. Widespread tissue damage and iNKT cell activation is produced in sickle cell anemia by rigid red cells that cause widespread microvascular occlusion and ischemia. NY1DD mice with sickle cell anemia have increased activation of iNKT cells, and high tissue levels of IFNγ and IFNγ-inducible chemokines (CXCL9, CXCL10 and CXCL11) that are chemotactic to activated lymphocytes that express CXCR3[64]. Treating NY1DD mice with anti-CD1d antibody to inhibit CD1d-restricted iNKT cell activation reverses pulmonary dysfunction and blocks the accumulation of activated leukocytes. Neutralization of CXCR3 receptors also ameliorates pulmonary dysfunction[64]. Infusion of an A_{2A} receptor agonist into NY1DD mice blocks iNKT IFNγ production, lung inflammation and lung injury[8]. CXCR3 also regulates NK- and T-cell trafficking during sepsis, and blockade of CXCR3 attenuates the pathogenesis of septic shock[65]. $A_{2A}R$ activation also can reduce inflammation and improve survival of mice with sepsis[66].

Effects of CD73 on lymphocyte migration into lymph nodes

CD73 is expressed on the cell surface of endothelial cells. After an inflammatory stimulus, lymphocyte migration into draining lymph nodes increases dramatically to facilitate the encounter of naive T cells with antigen-loaded dendritic cells. Cd73-/- mice have 2.5-fold increased rates of L-selectin-dependent lymphocyte migration from the blood through high endothelial venules compared with wild-type mice after LPS administration[67]. The endothelial $A_{2B}R$ is a likely target of CD73-generated adenosine and inhibits the adhesion of lymphocytes[67] and other leukocytes[68, 69].

Effects of CD73 on allograft survival

In a heterotopic cardiac allotransplantation model, CD73 deficiency in either donor or recipient mice results in decreased graft survival and development of cardiac allograft vasculopathy, suggesting a contribution of CD73 on both graft-resident and circulating cells in preventing vasculopathy[70]. Lack of CD73 results in loss of cardiac graft barrier function and diminished graft expression of $A_{2B}R$ mRNA, with a concordant exacerbation of acute inflammatory and immune responses. Antagonism of the $A_{2B}R$ causes a significant increase in vascular leakage, and activation of $A_{2B}Rs$ results in prolongation of graft survival and suppression of cardiac allograft vasculopathy. In another model, implantation of tracheal allografts from wild type mice into CD73-/- recipients caused a large increase in airway luminal obliteration that was associated with an increase in $CD3^+$ lymphocytic infiltration[71]. The protective effect of CD73 was attributed to generation of adenosine and stimulation of the $A_{2A}R$. Treatment of WT recipients with an $A_{2A}R$ agonist significantly reduced CD3+ lymphocyte infiltration and airway luminal obliteration; similar treatment of CD73-/-

recipients rescued them from rejection. These data implicate CD73 acting through adenosine generation and its stimulation of A_{2A} and A_{2B} receptors as inhibitors of lymphocyte recruitment into allografts. In allo-mismatched *in vitro* co-culture experiments either genetic deletion or pharmacological blockade of CD73 increased transendothelial lymphocyte migration. These data suggest that CD73 on graft-resident or circulating cells diminishes transendothelial leukocyte trafficking and mitigates inflammation and rejection.

Summary

Adenosine generally inhibits the activation and extravasation of lymphocytes into damaged or infected tissues. This is due to a combination of effects on T cells, APCs, and endothelial cells. A_{2A} and A_{2B} receptors and enzymes that control adenosine metabolism can be rapidly induced in response to inflammation or hypoxia. Adenosine signaling functions to limit inflammation and tissue injury without producing excessive immunosuppression.

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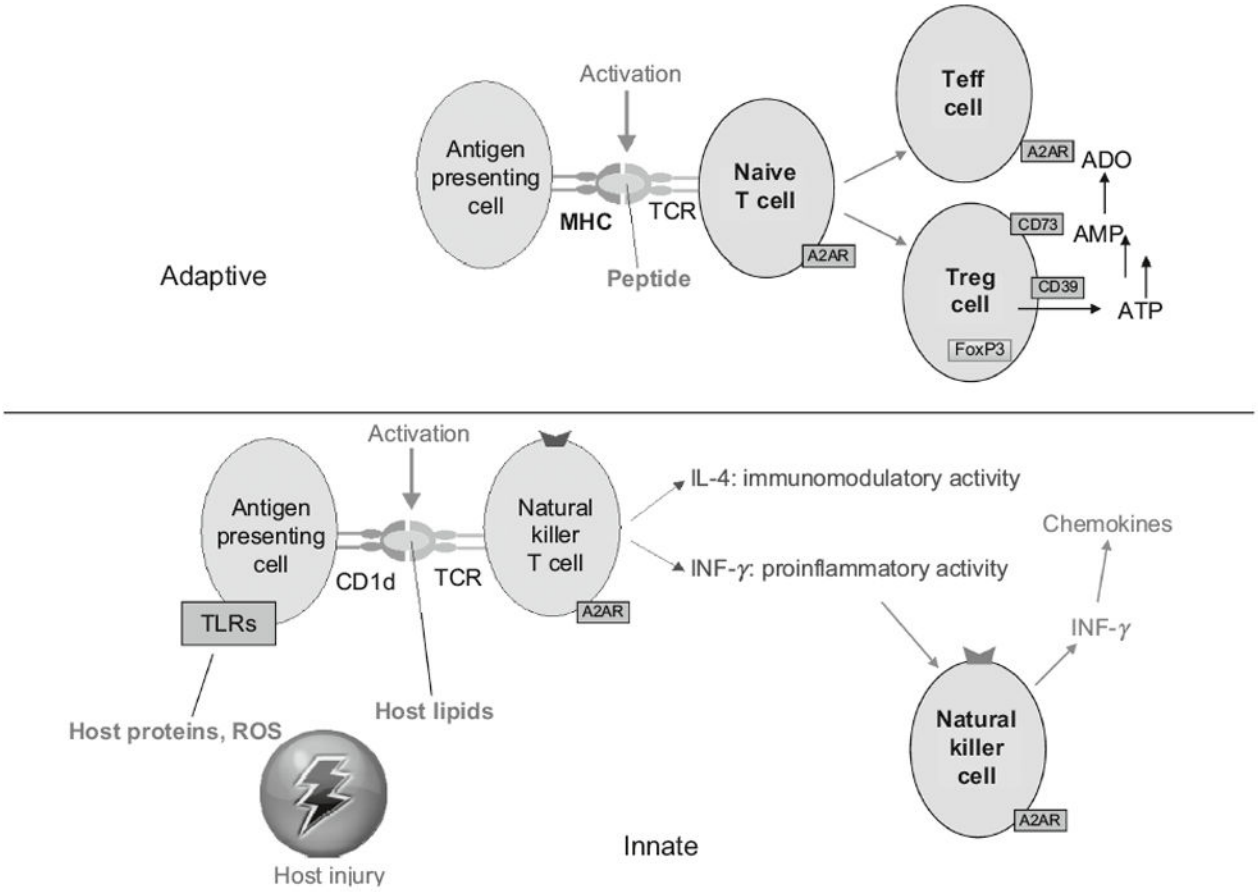

Figure 1. Cyclic AMP signaling inhibits TCR and CD28 signaling in lymphocytes

Cyclic AMP accumulates in T cells in the region of lipid rafts in response to TCR activation, and more globally in response to strong Gs-coupled $A_{2A}R$ activation. Cyclic AMP inhibits proximal TCR signaling through a pathway involving activation of protein kinase A-1 (PKA-1) and C-terminal Src kinase (Csk) to inhibit lymphocyte-specific protein kinase (Lck) and to reduce recruitment to CD3 of zeta-chain-associated protein kinase 70 (zap-70). PKA-1 also phosphorylates (indicated by *red dots*) and inhibits NF-AT. NF-AT activation is reversed by the Ca^{2+}-calmodulin-dependent phosphatase, calcineurin. TCR-induced accumulation of cAMP near lipid rafts is reduced upon CD28 stimulation due to the activation of phosphatidylinositol-3-kinase (PI3-K) to produce PIP3. This results in translocation from the cytosol to the lipid raft of a complex consisting of AKT, PDE4 and β-arrestin (β-arr) by binding of the plextrin homology (PH) domain of AKT to PIP3. PDE4 degrades cAMP to relieve inhibition of TCR signaling. Abbreviations: $A_{2A}R$, adenosine A_{2A} receptor; Ado, adenosine; Ino, inosine; ADA, adenosine deaminase; $\alpha_s\beta\gamma$, subunits of the heterotrimeric G protein, Gs; AC, adenylyl cyclase; AKT, a serine/threonine-specific protein kinase, also known as protein kinase B; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PDE4, type 4 phosphodiesterase; MHC, major histocompatibility complex; Ag, antigen; RhoH, Ras Homolog, a small GTP hydrolyzing protein; AKAP, A kinase anchor protein; TCR, T cell receptor; LAT, linker for activation of T cells; PLC,

phospholipase C; PKC, protein kinase C; CaM, calmodulin; NF-AT, nuclear factor of activated T cells; CREB, cAMP response element-binding protein.

Table 1

Enzymes involved in adenosine transport or metabolism

Human gene	Protein	alias	substrate	Human gene location
ADA	ADA		Ado/2-deoxyado	20q13.12
ADK	ADK		Ado/nucleosides	10q22.2
DPP4	DPP4	CD26	ADA binding	2q24.2
ENTPD1	ENTP1	CD39	ATP/ADP	10q24.1
ENTPD2	ENTP2	CD39L1	ATP/GTP	9q34.3
ENTPD3	ENTP3	CD39L3	ATP/ADP	3p22.1
NT5E	5NTD	CD73	AMP nucleotides	6q14.3
SLC29A(1-4)	S29A(1-4)	ENT(1-4)	ado	6p21.1/11q13/10q22.1/7p22.1
SLC28A(1-3)	S28A(1-3)	CNT(1-3)	ado	15q25.3/15q15/9q21.33

ADA, adenosine deaminase; ADK, adenosine kinase; Ado, adenosine; SLC28, solute carrier family 28 (sodium-coupled nucleoside transporter); ENTPD, ectonucleoside triphosphate diphosphohydrolase; DPP, dipeptidyl-peptidase; SLC29, solute carrier family 29 (nucleoside transporter); ENT, equilibrative nucleoside transporter; 5NTD, 5′ nucleotidase.